

Award Number: W81XWH-14-1-0441

TITLE: Identifying Determinants of PARP Inhibitor Sensitivity in Ovarian Cancer

PRINCIPAL INVESTIGATOR: Neil Johnson, Ph.D.

CONTRACTING ORGANIZATION:

Institute for Cancer Research
Philadelphia, PA 19111

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PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

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14. ABSTRACT Cells that are deficient in homologous recombination (HR) DNA repair, such as those lacking functional BRCA1 are highly sensitive to poly(ADP-ribose) polymerase (PARP) inhibitors. Ovarian cancer patients that harbored germ-line <i>BRCA1</i> mutations treated with PARP inhibitors exhibited meaningful responses in early phase clinical trials. However, emerging clinical trial data indicates that PARP inhibitor therapy may benefit only a subset of <i>BRCA1</i> mutation carriers. We hypothesized that a range of common ovarian cancer predisposing germ-line <i>BRCA1</i> gene mutations produce semi-functional proteins that are capable of providing PARP inhibitor resistance. <i>Specific Aims</i> . 1: Identify the region of mutant BRCA1 protein critical for PARP inhibitor resistance; 2: Identify genetic alterations essential for PARP inhibitor resistance; 3: Determine the ability of identified genetic aberrations to serve as predictive biomarkers. We discovered that multiple truncated BRCA1 proteins are semi functional and can promote HR and chemotherapy resistance. However, when we examined BRCA1 for regions that are absolutely critical for function, we found that the retention of the coiled-coil domain and PALB2 interaction is essential for BRCA1 activity in HR and therapy resistance. Our data support the notion that loss of large regions of BRCA1 can be tolerated for DNA repair and PARPi resistance. However, loss of the BRCA1-PALB2 interaction is critical for BRCA1 protein function, HR and PARPi resistance. Additionally, we have started our work examining exome sequences and gene expression in PARPi sensitive and resistance cancer cell lines. I attended and presented my work at the Marsha Rivkin biannual Meeting in Seattle.					
15. SUBJECT TERMS Ovarian cancer, BRCA1, RAD51, PARP inhibitors, platinum, biomarkers, drug resistance					
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1. INTRODUCTION:

Cells that are deficient in homologous recombination (HR) DNA repair, such as those lacking functional BRCA1 are highly sensitive to poly(ADP-ribose) polymerase (PARP) inhibitors. Ovarian cancer patients that harbored germ-line *BRCA1* mutations treated with PARP inhibitors exhibited meaningful responses in early phase clinical trials. However, emerging clinical trial data indicates that PARP inhibitor therapy may benefit only a subset of *BRCA1* mutation carriers. We hypothesize that a range of common ovarian cancer predisposing germ-line *BRCA1* gene mutations produce semi-functional proteins that are capable of providing PARP inhibitor resistance. Our preliminary data suggests that PARP inhibitor selection pressure results in genetic adaptations that enable cells to utilize severely truncated BRCA1 proteins for RAD51 loading and HR repair. Our objectives are to define the BRCA1 peptide region minimally required for PARP inhibitor resistance, and discover genetic alterations that activate DNA end resection as well as mutant *BRCA1* protein stabilization in ovarian carcinomas. The expression of mutant BRCA1 or novel proteins identified to be important for drug resistance will be assessed for their ability to be used as biomarkers of PARP inhibitor or platinum response. *Specific Aims.* 1: Identify the region of mutant BRCA1 protein critical for PARP inhibitor resistance; 2: Identify genetic alterations essential for PARP inhibitor resistance; 3: Determine the ability of identified genetic aberrations to serve as predictive biomarkers. Protein expression in tumors will be assessed for their potential to serve as biomarkers that predict PARP inhibitor or platinum response.

1. KEYWORDS:

Ovarian cancer, BRCA1, RAD51, PARP inhibitors, platinum, biomarkers, drug resistance.

2. ACCOMPLISHMENTS:

What were the major goals of the project?

Major Task 1: Determine the minimum region of BRCA1 protein required for PARP inhibitor resistance.

Milestone(s) Achieved: Drug resistant cell lines are derived that express different types of mutant BRCA1 proteins. Target date for completion: 12 months (from start of award). Current status: 100% completed.

Major Task 2: Determine the minimum region of BRCA1 protein required for RAD51 focus formation.

Milestone(s) Achieved: The minimum region of mutant BRCA1 protein is identified that can contribute to RAD51 loading. Target date for completion: 16 months (from start of award). Current status: 100% completed.

Major Task 3: Generate whole exome sequencing and gene expression data sets for PARP inhibitor sensitive and resistant cell lines.

Milestone(s) Achieved: Identification of genes that are mutated or differentially expressed in PARP inhibitor resistant cells. Target date for completion: 30 months (from start of award). Current status: 50% completed. Expected completion date: 30 months.

Major Task 4: Validate identified genes as resistance causing through RNAi and cDNA overexpression techniques.

Milestone(s) Achieved: Validation of genes that are mutated or differentially expressed and result in PARP inhibitor resistance. Target date for completion: 36 months (from start of award). Current status: 0% completed. Expected completion date: 36 months.

Major Task 5: Obtain IRB approval for assessing tumor DNA and assembling tumor microarrays.

Milestone(s) Achieved: IRB protocol approved. Target date for completion: 40 months (from start of award). Current status: 100% completed.

Major Task 6: Analyze tumor DNA for mutations.

Milestone(s) Achieved: Identification of gene mutation or protein expression changes in ovarian tumors. Target date for completion: 55 months (from start of award). Current status: 0% completed. Expected completion date: 55 months.

Major Task 7: Determine the ability of potential biomarkers to predict therapeutic outcome.

Milestone(s) Achieved: Biomarkers are ready for application in clinical trials of BRCA1 mutant ovarian cancer and data is published in peer-reviewed journals. Target date for completion: 60 months (from start of award). Current status: 0% completed. Expected completion date: 60 months.

What was accomplished under these goals?

Major Task 1: Determine the minimum region of BRCA1 protein required for PARP inhibitor resistance.

In Aim 1 of our OCRP award, we examined a *BRCA1* mutant cancer cell line panel for the expression of truncated BRCA1 proteins. As expected, cell lines that harbored frameshift *BRCA1* mutations did not produce a full-length BRCA1 protein. However, L56-BRC1, SUM149PT and UWB1.289 cell lines that harbored mutations within exon 11 of the *BRCA1* gene were capable of expressing the BRCA1- Δ 11q splice isoform that lacks amino acids 263-1365. SUM1315MO2, HCC1395 and MDA-MB-436 cell lines that harbored *BRCA1* mutations in N- and C-terminally located regions did not have detectable truncated BRCA1 protein expression (**Fig. 1**).

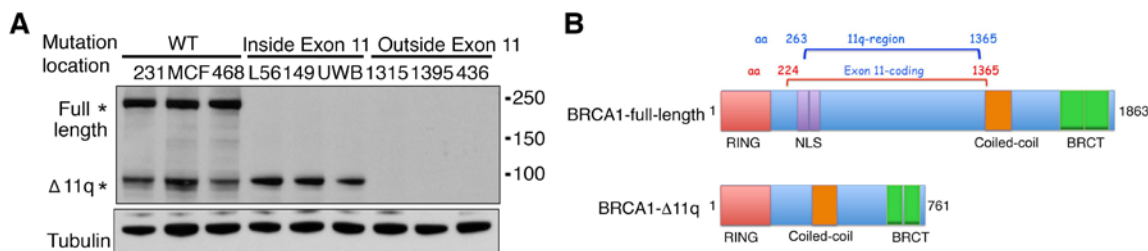


Figure 1. *BRCA1* exon 11 mutant cell lines express the truncated BRCA1- Δ 11q isoform. (a) MDA-MB-231 (231), MCF7 (MCF), MDA-MB-468 (468), L56-BRC1 (L56), SUM149PT (149), UWB1.289 (UWB), SUM1315MO2 (1315), HCC1395 (1395), MDA-MB-436 (436) cell lines were analyzed for BRCA1 by Western blot. *Predicted BRCA1 locations, molecular weights are indicated. (b) Diagrammatic representation of BRCA1 full-length and the regions that are lost in the truncated BRCA1- Δ 11q protein.

We examined the impact of loss of the large BRCA1 central region amino acids 263-1365 on chemotherapy responsiveness. In cell growth experiments, *BRCA1* wild-type cells expressing the full-length protein that were continuously cultured in the presence of PARPi or cisplatin proliferated at the same rate as vehicle treated cells. Cells that expressed the BRCA1- Δ 11q protein proliferated at a reduced rate, and cell lines with no detectable truncated BRCA1 protein expression lost viability in the presence of PARPi or cisplatin (**Fig. 2**). Additionally, *BRCA1* wild-type as well as BRCA1- Δ 11q expressing cell lines all formed robust BRCA1 and RAD51 γ -irradiation-induced foci (IRIF). Depletion of the BRCA1- Δ 11q using shRNAs reduced RAD51 IRIF and sensitized cells to PARPi and cisplatin treatments (data not shown, see Wang et. al., *Canc Res* for more details). These data indicate that despite lacking over half of all the amino acids present in the central region of full length BRCA1, the BRCA1- Δ 11q protein was functional, promoting HR and chemotherapy resistance.

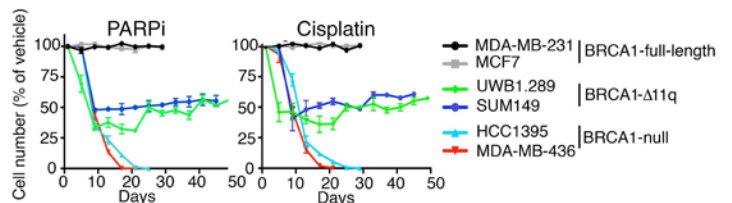


Figure 2. *BRCA1*-11q expressing cells have intermediate chemo-sensitivity. Cells were maintained in the presence of vehicle, rucaparib or cisplatin. Growth was expressed as a percentage of vehicle treated cells.

We next compared the ability of ectopic BRCA1 proteins to rescue PARPi and cisplatin sensitivity (**Fig. 3A**). MDA-MB-436 cells harbor a *BRCA1*^{5396+1G>A} mutation resulting in protein misfolding, undetectable BRCA1 and RAD51 IRIF, and exquisite chemo-sensitivity. MDA-MB-436 cells expressing BRCA1-full-length demonstrated robust PARPi and cisplatin resistance. BRCA1- Δ 11q was less effective at rescue than full-length BRCA1, but

cells were significantly more resistant to PARPi and cisplatin compared to mCherry control cells (**Fig. 3B**). To determine the BRCA1 peptide region that is most critical for BRCA1 activity, we introduced an L304P mutation in the coiled-coil region of the protein that blocks BRCA1-PALB2 interaction (equivalent to L1407P in full-length BRCA1). Here, preventing the BRCA1-PALB2 interaction completely abolished BRCA1- $\Delta 11q$ mediated-PARPi and cisplatin rescue (**Fig. 3B**). These data suggest that retention of the coiled-coil domain and PALB2 interaction is essential for BRCA1 activity in HR and therapy resistance.

We also confirmed the ability of BRCA1- $\Delta 11q$ expression to rescue therapy sensitivity *in vivo*. Here, rucaparib and cisplatin significantly delayed growth in MDA-MB-436 xenografts expressing mCherry. In contrast, rucaparib and cisplatin had minimal impact on BRCA1 full-length and BRCA1- $\Delta 11q$ expressing tumors (**Fig. 3C**). Additional details of this work can be found in our recent publication (Wang *et al.*, *Cancer Research*, 2016). Furthermore, we demonstrated that BRCA1 truncated proteins lacking the C-terminal BRCT or N-terminal RING domains of BRCA1 were also capable of promoting therapy resistance (Johnson *et al.*, *PNAS* 2013; Wang *et al.*, *JCI* 2016).

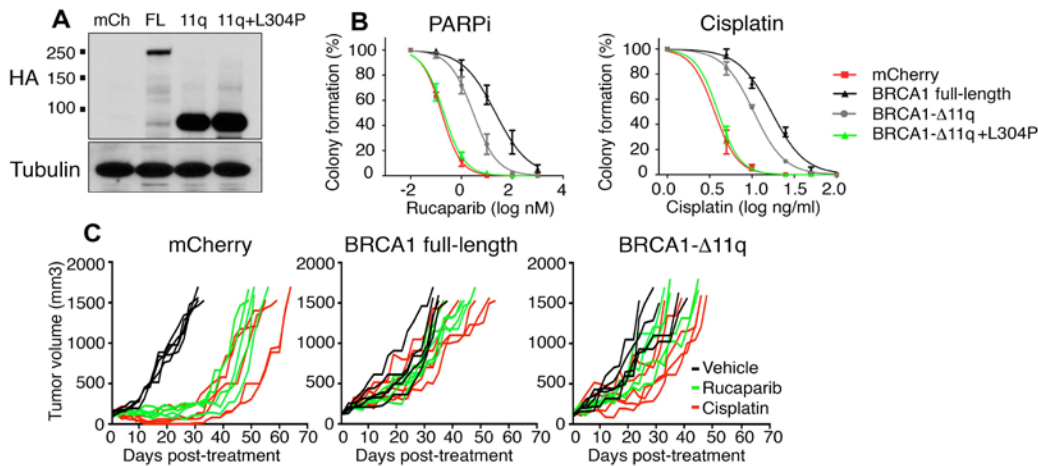


Figure 3. BRCA1- $\Delta 11q$ provides resistance to therapy. (a) MDA-MB-436 cells expressing mCherry, BRCA1 full-length, BRCA1- $\Delta 11q$ or BRCA1- $\Delta 11q$ +L304P were assessed for BRCA1 protein expression by Western blot. (b) Cells described in (a) were treated with rucaparib or cisplatin and colony formation assessed. (c) MDA-MB-436 tumor xenografts expressing mCherry, BRCA1 full-length or BRCA1- $\Delta 11q$ were treated with vehicle (black), rucaparib (green) or cisplatin (red), lines represent individual tumors.

Because BRCA1- $\Delta 11q$ activity was abolished when we introduced a mutation that prevented BRCA1-PALB2 interaction, we investigated the importance of this interaction in full-length as well as additional truncated forms of BRCA1. Introduction of the L1407P mutation that prevents BRCA1-PALB2 interaction into full-length BRCA1 also completely abrogated the ability of cells to form colonies in the presence of rucaparib. Furthermore, the residual activity and PARPi resistance provided by other truncated forms of BRCA1, including Δ RING and Δ BRCT proteins, was abolished by the L1407P mutation (**Fig. 4**). In summary, these data support the notion that loss of large regions of BRCA1 can be tolerated for DNA repair and PARPi resistance. However, loss of the BRCA1-PALB2 interaction is critical for BRCA1 protein function, HR and PARPi resistance.

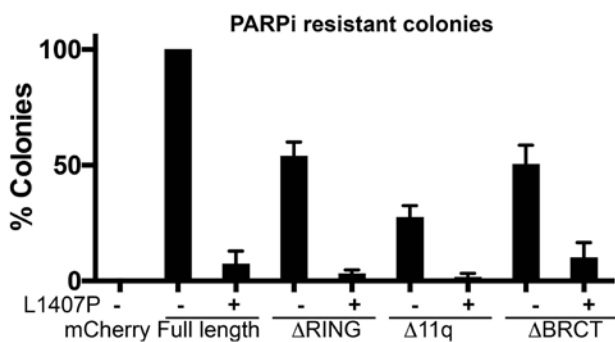
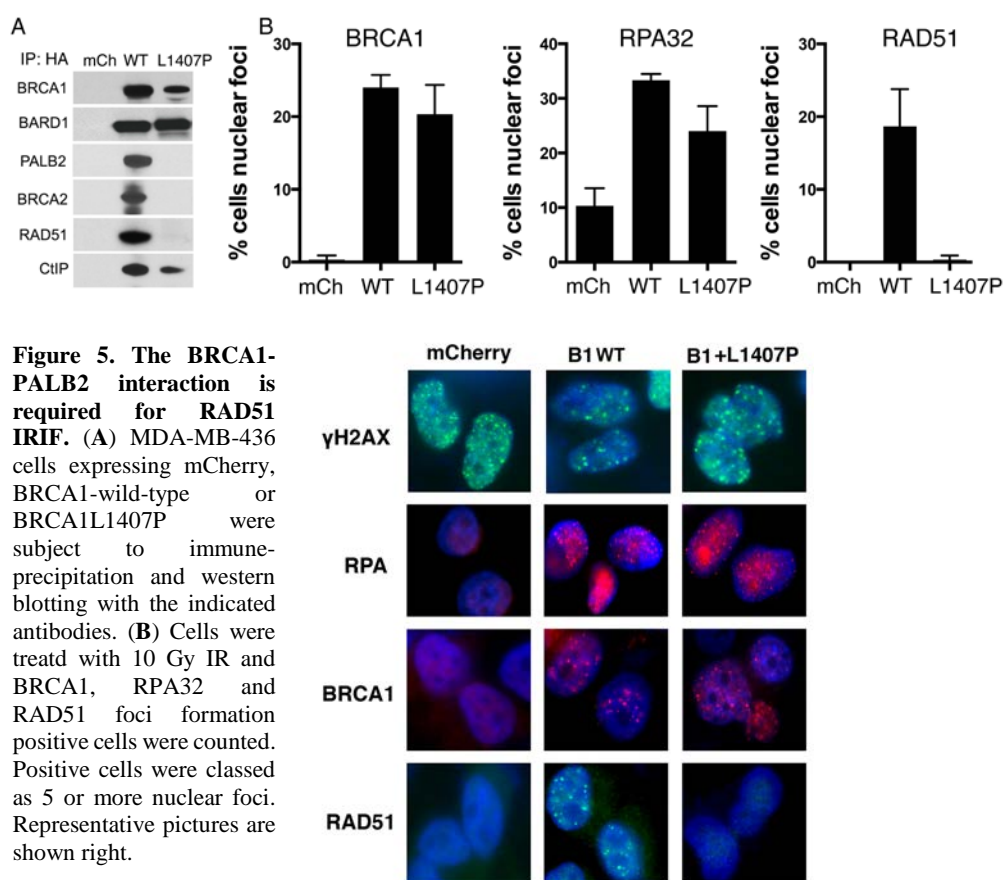


Figure 4. The BRCA1 L1407P missense mutation abolishes the ability of BRCA1 proteins to promote PARPi resistance. MDA-MB-436 cells expressing mCherry, BRCA1-full-length, BRCA1- Δ RING, BRCA1- $\Delta 11q$, or BRCA1- Δ BRCT domains that harbored wild-type (-) or L1407P (+) coiled-coil peptide mutations were assessed for PARPi resistant colony formation. Cells were grown in the presence of rucaparib for 3 weeks until resistant colonies emerged. Resistant colonies are expressed as a percentage of colonies arising in full-length BRCA1 expressing cells.

Major Task 2: Determine the minimum region of BRCA1 protein required for RAD51 focus formation.

To confirm that BRCA1 constructs interacted with the expected proteins, we carried out immunoprecipitation of HA-BRCA1 and measured the protein-protein interactions present in BRCA1 wild-type and BRCA1^{L1407P} expressing cells by Western blotting. Wild-type BRCA1 interacted with all expected proteins. In line with previous reports, although BRCA1^{L1407P} interacted with N- and C-terminal binding proteins BARD1 and CtIP, but was unable to bind PALB2 and consequently BRCA2 and RAD51 that are components of the B1-P2-B2-R1 complex (Fig. 5A). To measure the effects of the BRCA1^{L1407P} mutation on steps of HR DNA repair, we carried out immunofluorescence assays to measure BRCA1, RPA32 and RAD51 IRIF. BRCA1^{L1407P} was equally efficient as BRCA1 wild-type at forming IRIF. Additionally, we measured RPA32 foci formation as an indicator of DNA end resection, the first step of HR. Here, BRCA1^{L1407P} was also as effective as BRCA1 wild-type at promoting RPA32 foci and DNA end resection, likely due to intact BRCA1-CtIP complex formation. However, while BRCA1 wild-type effectively promoted RAD51 foci formation, cells expressing BRCA1^{L1407P} had undetectable RAD51 foci (Fig. 5B). These data indicate that the BRCA1-PALB2 complex is essential for RAD51 loading and the completion of HR DNA repair.



Major Task 3: Generate whole exome sequencing and gene expression data sets for PARP inhibitor sensitive and resistant cell lines.

To date, we have started our work examining exome sequences and gene expression in PARPi sensitive and resistance cancer cell lines. Cell lines have been collected and subject cells to RNA-seq and exome sequencing. We are currently in the data analyses phase and will be ready to report our results in year 3 report in line with our SOW.

What opportunities for training and professional development has the project provided?

During the second year of this award, I have taken part in the following training activities:

- Discussed progress with Drs. Boyd and Golemis.
- Discussed progress with my Chief Scientific Officer Dr. Chernoff.
- Attended Junior Faculty Mentoring Meetings.
- Presented research at the monthly Faculty Seminar.
- Presented research at Molecular Therapeutics Departmental meetings.
- Presented research at FCCC gynecologic oncology meetings.

During the second year of this award, I have taken part in the following professional development activities:

- I frequently attend FCCC Gynecologic Cancer Meetings
- I attended and presented my work at the Marsha Rivkin biannual Meeting in Seattle
- I attended the Ovarian Cancer Academy Meeting in Seattle
- I attended the AACR Advances in Ovarian cancer meeting in Orlando.
- I attended Bassett Center for BRCA annual symposium, Philadelphia
- I have submitted NIH and DoD grant applications
- I have published my work in peer-reviewed journals

How were the results disseminated to communities of interest?

I have presented my work to FCCC meeting groups described above. Additionally, I have presented my work at the Marsha Rivkin biannual meeting. Furthermore, our work was published in Cancer Research and Journal of Clinical Investigation.

What do you plan to do during the next reporting period to accomplish the goals?

In the next reporting period, we will analyze whole exome sequencing and gene expression data sets for PARP inhibitor sensitive and resistant cell lines and generate a defined list of hits. The goal is to identify genes that work with hypomorphic BRCA1 proteins, such as 53BP1, to promote DNA repair and PARP inhibitor resistance. Additionally genes that have deregulated expression or are mutated will be manipulated using RNAi or CRISPR/Cas9 and their biological functions defined. We will examine the impact of genes on RPA32 and RAD51 foci formation as markers of DNA end resection and RAD51 loading during homologous recombination, respectively. We will also begin to generate IRBs so that we can examine the expression of proteins of interest in ovarian cancer patient tumors.

3. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

We have discovered that multiple truncated BRCA1 proteins can contribute to HR DNA repair and PARPi resistance. Additionally, we have defined that the ability of BRCA1 to interact with PALB2 is most critical for its function. This work could help determine which patients will gain most benefit from PARPi therapy and which patients will quickly develop resistance. Further work is required to confirm these observations in the clinical setting.

What was the impact on other disciplines?

Nothing to Report.

What was the impact on technology transfer?

Nothing to Report.

What was the impact on society beyond science and technology?

Nothing to Report.

4. CHANGES/PROBLEMS:

Nothing to Report.

5. PRODUCTS:

Nothing to Report.

6. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	<i>N. Johnson, Ph.D.</i>
Project Role:	Principal Investigator
Researcher Identifier (e.g. ORCID ID):	Neiljohn
Nearest person month worked:	6
Contribution to Project:	Overall administration and guidance of research; Management and training of personnel
Funding Support:	N/A
Name:	<i>J. Boyd, Ph.D.</i>
Project Role:	Mentor
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to Project:	Dr. Boyd is the mentor on this project. He provides advice, assistance and support.
Funding Support:	N/A
Name:	<i>J. Kraiss, Ph.D.</i>
Project Role:	Postdoctoral Associate
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	12
Contribution to Project:	Dr. Kraiss contributed to the cell culture and molecular biology experiments.
Funding Support:	Salary support by NIH T32
Name:	<i>J. Nascon</i>
Project Role:	Graduate Student
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	6
Contribution to Project:	Mr. Nascon assists with the cell culture and molecular biology experiments.
Funding Support:	N/A

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

- *Please see Other Support attached.* Changes from the last reporting period are marked with a line in the right hand margin.

What other organizations were involved as partners?

Organization Name: Florida International University

Location of Organization: Miami, Florida

Partner's contribution to the project: Mentor

- Dr. Boyd devotes 10% effort as a mentor on this project. Funds are also allotted for travel.

Organization Name: Temple University

Location of Organization: Philadelphia, PA

Partner's contribution to the project: Consultant

- Dr. Burger provided advice and guidance on the development of biomarkers that predict tumor PARP inhibitor sensitivity. His role will increase in the upcoming years.

Organization Name: University of Washington

Location of Organization: Seattle, WA

Partner's contribution to the project: Consultant

- Dr. Swisher will provided advice and guidance on the development of on the biomarkers that predict tumor PARP inhibitor sensitivity. Her role will increase in the upcoming years.

7. SPECIAL REPORTING REQUIREMENTS

- **COLLABORATIVE AWARDS:** Not Applicable.
- **QUAD CHARTS:** Not Applicable.

8. APPENDICES: Not Applicable.

Other Support

Johnson, Neil

ACTIVE

R21 CA191690 (PI: Johnson)	3/17/2015 - 2/28/2017	20.0%
NIH	\$132,520	2.40 calendar

Identifying BRCA1 Protein Variants that Provide Resistance to Therapy

The major goals of this project are: 1) To identify BRCA1 isoforms highly expressed in drug resistant tumors; and 2) To determine the ability of BRCA1 isoforms to provide HR DNA repair and drug resistance.

Procuring Contracting/Grants Officer: Candace Cofie, 9609 Medical Center Dr., Bethesda, MD 20892, 240-276-6317

W81XWH-14-1-0441 (PI: Johnson)	9/15/2014 - 9/14/2019	50.0%
DOD	\$135,496 (Partial Salary)	6.00 calendar

Identifying Determinants of PARP Inhibitor Sensitivity in Ovarian Cancer

The major goals of this project are: 1) To identify the region of mutant BRCA1 protein critical for PARP inhibitor resistance; 2) To identify genetic alterations essential for PARP inhibitor resistance; and 3) To determine the ability of identified genetic aberrations to serve as predictive biomarkers.

Procuring Contracting/Grants Officer: Kevin Moore, USAMRAA, 820 Chandler Street, Fort Detrick, MD 21702, 301-719-7101

W81XWH-15-1-0197 (PI: Johnson)	7/1/2015 - 6/30/2017	15.0%
DOD	\$152,164	1.80 calendar

Determine the Impact of Novel BRCA1 Translation Start Sites on Therapy Resistance in Ovarian Cancer

The major goals of this project are: 1) To identify germline BRCA1 mutations capable of generating drug resistance-inducing N-terminal deficient proteins; 2) To characterize the role of N-terminal deficient BRCA1 proteins in the DNA damage response; and 3) To identify small molecules that kill N-terminal deficient BRCA1 protein expressing cells.

Procuring Contracting/Grants Officer: Ayi Ayayi, USAMRAA, 820 Chandler St., Fort Detrick, MD 21701, 301-619-4018

COMPLETED

Komen, CCR12226280

OVERLAP

None

Other Support

Krais, John

ACTIVE

W81XWH-14-1-0441 (PI: Johnson)	9/15/2014 - 9/14/2019	100.0%
DOD	Partial Salary	12.00 calendar
Identifying Determinants of PARP Inhibitor Sensitivity in Ovarian Cancer		
The major goals of this project are: 1) To identify the region of mutant BRCA1 protein critical for PARP inhibitor resistance; 2) To identify genetic alterations essential for PARP inhibitor resistance; and 3) To determine the ability of identified genetic aberrations to serve as predictive biomarkers.		
Procuring Contracting/Grants Officer: Kevin Moore, USAMRAA, 820 Chandler Street, Fort Detrick, MD 21702, 301-719-7101		

T32 CA009035 (PI: Chernoff)	9/15/2016 - 8/31/2021	NA
NIH	Stipend only	
Training Program in Cancer Research (Trainee: 5/25/15-5/24/17)		
The overall goal of this program is to prepare postdoctoral scientists for independent careers in basic and/or translational research focused on cancer.		

COMPLETED

None

OVERLAP

None